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Do febrile seizures improve memory?

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In this issue of *Neurology*, Chang et al.[1] present a population-based study on the effects of febrile seizures on working memory, and find that school-aged children with febrile seizures performed significantly better than randomly selected, population-based control subjects. However, children with the onset of febrile seizures before the age of 1 year had deficits in learning, consolidation, and delayed recognition.

This article extends prior work on this cohort,[2] which found that these school-aged children, except for those with seizure onset under 1 year of age, performed better than population-based control subjects on measures of intelligence and academic achievement. The new results published in the current article are of particular interest because they focus specifically on learning and memory aspects, which require an intact hippocampus. In both humans[3,4] and immature animal models,[5,6] prolonged febrile seizures have been associated with acute hippocampal injury. Furthermore, a history of prolonged febrile seizures is commonly elicited in individuals with a specific pattern of chronic hippocampal injury, mesial temporal sclerosis,[3,4,7–9] and mesial temporal lobe epilepsy, which are often associated with impaired memory functions.[10–13]

Prior epidemiologic studies of the outcome of febrile seizures in both United States[14] and the United Kingdom[15,16] also have not found differences in global cognitive outcomes between children with febrile seizures and either siblings[14] or population controls,[15,16] but these studies did not specifically examine memory. Interestingly, seizure onset before 1 year of age was also a risk factor for poor outcome in the recent British study.[16] The current study adds reassuring data that memory tasks, which are a more specific indicator of hippocampal function, are preserved in the majority if children with febrile seizures, but raises concern regarding those children who experience these seizures during the first postnatal year.

Why be concerned specifically about memory and related hippocampal functions in children with febrile seizures, and what factors might underlie the deficits noted specifically in individuals experiencing the seizures during infancy? Both human[3] and animal[5,6,17] data have suggested recently that at least transient injury to hippocampus and related limbic structures can occur in individuals with prolonged febrile seizures. In human studies, prospective data using neuroimaging methods demonstrated acute swelling of hippocampus after prolonged febrile seizures.[3] In an infant rat model of prolonged (20-minute) febrile seizures, cytoskeletal changes in neurons were evident within 24 hours and persisted for several weeks, without leading to cell loss.[5] However, persistently altered functional

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properties of these injured neurons were evident.[17,18] Thus, it is conceivable that the exposure of hippocampal neurons to febrile seizures early in life, and particularly during infancy, may lead to transient injury and more sustained dysfunction of these cells. These effects may be age dependent, and more pronounced during the first postnatal year. The strength of the study by Chang et al.[1] is its focus on well-defined, sophisticated measures of hippocampal-dependent working memory function, allowing relatively subtle deficits to be detected.

An unusual finding of this study is that children with febrile seizures actually performed better than the control subjects. The authors offer some interesting theoretical speculations as to why this might be the case. However, it would be premature to tell parents that the febrile seizure, far from harming their child, was actually beneficial. In their prior report,[2] the authors found that these same children also scored higher than population controls on tests of intelligence and academic achievement, which is at odds with a number of well-designed larger studies that—while finding no adverse effect of febrile seizures—did not find an improvement.[14–16] Therefore, the “take home” message from these new data should be that most febrile seizures do not adversely affect global measures of intelligence, nor do they harm more specific hippocampal functions such as memory, in children older than 1 year of age.

Although this report is a valuable contribution, many questions remain unanswered. The authors did not find significant differences in memory between children with complex and simple febrile seizures. Some studies have found adverse outcomes on intelligence in children with prolonged febrile seizures,[19] though others have not.[14–16] Because Chang et al.[1] had 87 children with febrile seizures, the number with prolonged febrile seizures was relatively small. Approximately 10% of all febrile seizures last more than 15 minutes, and 5% last 30 minutes or longer.[20] Because simple febrile seizures have not been associated with hippocampal injury in either human or animal data, future research should focus on memory and other hippocampal-dependent functions in children who experience prolonged febrile seizures. Chang et al.[1] demonstrate the feasibility of such studies. We now need large-scale investigations analyzing the contribution of seizure duration and the age of the child at seizure onset to specific outcome measures of learning and memory.

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